

# Pathology of Cat-Scratch Disease

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LEE FOSHAY<sup>12</sup> in 1932 was first to recognize a disease entity characterized by a primary skin lesion and regional lymph node enlargement following the scratch of a cat. His observations were not published. In a communication in 1952 he said that in 1945 Rose prepared an antigen from a diseased lymph node of a person who had this disease.<sup>13</sup> Later this antigen was used by Foshay as testing material on his own case. In 1950 Debre<sup>8</sup> published a report on this disease in France. Flores<sup>11</sup> cited the work of Petzetakis of Greece who in 1935 reported on the clinical and anatomical characteristics of this disease; and since that work antedated the publication of Debre, Flores called the entity *Petzetakis disease*. The first report in this country was that of Greer,<sup>16</sup> who in 1951 described a case in a young man. Positive skin reactions were obtained with an antigen supplied by Foshay. Since then many reports have appeared in this country (summarized in 1951, 1952 and 1954 by Daniels and MacMurray<sup>5, 6, 7</sup>) and in France, South Africa, Canada, Australia, England, Switzerland and Germany. In California several cases have been reported in scattered parts of the state (Cuttle,<sup>3</sup> Epstein,<sup>10</sup> Frank and Harder,<sup>14</sup> Gifford<sup>15</sup> and Todd<sup>25</sup>).

The clinical epidemiologic and etiologic features are well covered in the monographs of Daniels and MacMurray,<sup>5, 6, 7</sup> Mollaret and associates,<sup>19, 20, 21</sup> and Cuttle.<sup>3</sup> The disease is self limited, characterized by a primary skin lesion at the site of a scratch in most instances attributed to a cat, followed by swelling of regional lymph nodes after an interval of four days to a month. A fever of moderate degree may develop with malaise and loss of appetite. The nodes are tender and the skin may be reddened. The degree of enlargement varies, the nodes at times reaching 6 to 8 cm. in diameter. One or more regional nodes may be involved. Suppuration and sinus formation may occur although in milder forms the nodes may slowly involute without breaking down. The enlargement may persist for many months. A history of cat-scratch is obtained in the majority of cases. Dog bite, thorn scratch and rabbit bite have been reported as presumably the source of infection. In a small proportion of cases there is no history of skin injury. Complications are rare. Subcutaneous lesions suggestive of erythema nodo-

*• A pathologic and histogenetic study of material obtained from ten cases of cat-scratch disease was carried out. The earliest lesion was of ten days' duration and the oldest of 35 days' duration. The first changes in lymph nodes consisted of proliferation of epithelioid cells followed by exudation of leukocytes in their centers and subsequent necrosis of the exudate and epithelioid cells. Proliferative changes leading to formation of epithelioid cell tubercles were seen in some cases. Homogenization of necrotic centers brought about the formation of caseous tubercles similar to those seen in tuberculosis, syphilis, lymphogranuloma venereum and tularemia. Differentiation and the final diagnosis of cat-scratch disease rests upon correlation of histopathologic observations, clinical studies and specific skin tests.*

sum have been described.<sup>21, 24</sup> Cases in which Parinaud's oculoglandular syndrome occurred also have been reported.<sup>2, 9</sup> Mild encephalitis was reported by Stevens.<sup>24</sup> Blood findings are not diagnostic.

The diagnosis of cat-scratch disease is based on the history, clinical course and laboratory tests. Exclusion tests for infectious mononucleosis, brucellosis, tularemia, tuberculosis and lymphogranuloma venereum should be done in all cases. A complement fixation test using lygranum as the antigen has been utilized by Mollaret and his associates<sup>22</sup> with positive reactions, indicating the close relation of this disease and lymphogranuloma venereum. By far the most important test available at present is a skin test using a 1:5 saline solution dilution of heat-treated exudate obtained from suppurative lymph nodes of known cases. This antigen, although crude, appears highly specific. Daeschner<sup>4</sup> emphasized the specificity of this antigen and the absence of reaction in normal controls. This was confirmed by Bettley and Fairburn.<sup>1</sup> The skin reaction may remain positive for many years after recovery.

The cause of the disease is probably a virus, as yet not isolated, closely related to the psittacosis-lymphogranuloma venereum group. Mollaret and co-workers<sup>22</sup> were able to transmit the disease to monkeys but failed to grow the virus in tissue culture or transmit the disease to other animals. These investigators also described the presence of intra-

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TABLE 1.—Clinical data on ten cases of cat-scratch disease

Case	Sex and Age	History of Cat-Scratch	Primary Lesion	Site of Lymph Node Swelling	Duration of Swelling	Fever
1.	Male, 6 yrs.	Right hand	At site of scratch	Rt. axilla	35 days	None
2.	Female, 3½ yrs.	Numerous cat scratches	None	Rt. groin	30 days	Max. 102° F.
3.	Female, 53 yrs.	Numerous over arm	Right index finger	Rt. axilla	21 days	None
4.	Male, 60 yrs.	Repeated	Right hand	Rt. axilla	12 days	None
5.	Male, 35 yrs.	Numerous—both arms	Forefinger right hand	Lft. axilla	35 days	None
6.	Female, 42 yrs.	Many scratches	Left thumb	Sup. cubital nodes, lf.	10 days	Mild
7.	Female, 30 yrs.	Frequent cat scratches	None	Both inguinal nodes	27 days	Mild
8.	Female, 4 yrs.	No history of scratch	Right mandible	Angle of jaw	30 days	Mild
9.	Female, 43 yrs.	Frequent cat scratches	None	Rt. groin	21 days	Mild
10.	Male, 8½ yrs.	Cat-scratch of face	Left temple	Angle of lft. jaw	25 days	Slight

TABLE 2.—Laboratory data on ten cases of cat-scratch disease

Case	Frei Test	Tuberculin Test	Culture Lymph Node	—Skin Test— Cat-Scratch Antigen	Heterophil Antibody	—Agglutination Test— Tularensis	Brucella abortus	Blood Wassermann
1.	Neg.	Neg.	Neg.	3+	Neg.	Neg.	Neg.	Neg.
2.	Neg.	Neg.	Neg.	4+	Neg.	Neg.	Neg.	Neg.
3.	Neg.	Neg.	Neg.	2+	Neg.	Neg.	Neg.	Neg.
4.	Neg.	Neg.	Neg.	2+	Neg.	Neg.	Neg.	Neg.
5.	Neg.	2+	Neg.	3+	Neg.	Neg.	Neg.	Neg.
6.	Neg.	2+	Neg.	2+	Neg.	Neg.	Neg.	Neg.
7.	Neg.	Neg.	Neg.	4+	Neg.	Neg.	Neg.	Neg.
8.	Neg.	Neg.	Neg.	3+				
9.	Neg.	Neg.	Neg.	2+	Neg.	Neg.	Neg.	Neg.
10.	Neg.	Neg.	Neg.	3+	Neg.	Neg.	Neg.	Neg.

cytoplasmic inclusions which are similar to the elementary bodies and granular corpuscles of psittacosis. Wegmann<sup>26</sup> and Winship<sup>27</sup> expressed doubt that these intracellular granules are virus inclusion bodies.

As to the source of the etiological agent, little is known. Cats appear to be immune to inoculation and are usually healthy at the time of transmission of the disease. This fact prompted Mollaret to postulate that the cat serves to carry the disease from some other reservoir in nature, presumably birds. Much remains to be done to clarify problems of etiology and epidemiology.

The basis of the present communication is pathologic studies of lymph nodes and subcutaneous tissue in ten cases observed at Sutter Hospital in a period of 18 months. Eight additional cases of probable cat-scratch disease were observed but were not included in this study because they did not meet all the diagnostic criteria. In Tables 1 and 2 the pertinent clinical and laboratory data concerning these cases are given.

#### CLINICAL STUDIES

Only cases in which there were typical clinical history and positive reactions to skin testing with cat-scratch antigen were included in the present study. As was pointed out by Daniels and MacMurray,<sup>5</sup> weak or negative reactions to the antigen have been observed in cases of cat-scratch fever.

Four of the ten cases occurred in children under ten years of age; the oldest patient in the series was 60 years of age. On close questioning all gave a

history of intimate exposure to cats. Nine of the ten had been scratched by cats. In seven of the ten cases a primary skin lesion was present. The onset of regional lymph node enlargement followed the primary lesion in from one to three weeks. In two instances the inguinal nodes were involved, in five the axillary nodes, in two the cervical lymph nodes and in one the superficial cubital lymph node. All the patients had surgical removal of the affected lymph nodes. The time between the first sign of lymph node enlargement and operative removal varied from 12 to 35 days. Mild fever was observed in six cases. Malaise, headache and loss of appetite were noted in few cases. In the majority of cases constitutional symptoms were mild or absent. Reports of blood counts were not included since they were not of diagnostic value. Slight leukocytosis (up to 14,000 cells per cubic millimeter) was reported, with slight rise in the percentage of neutrophils. Eosinophilia was not observed.

In all cases skin tests using Frei antigen (Lederle) gave negative reactions (Table 2). Tuberculin skin tests gave positive reactions in two patients. Cultures of involved lymph nodes were negative for bacteria and fungi. Heterophil antibody tests and agglutination tests with *Brucella abortus* and *Pasteurella tularensis* were negative. Results of Wassermann tests were negative in all cases. All patients had positive skin reaction to antigens of cat-scratch fever. With the exception of the patients in Cases 9 and 10, who were tested with an antigen prepared from one of the patients in the present series, these patients were tested with antigen supplied by Drs. Daniels

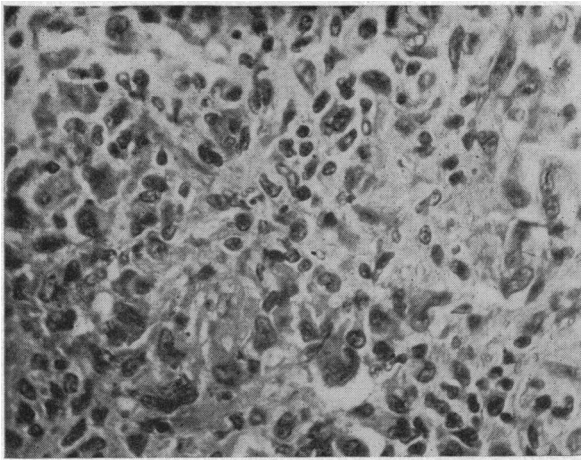


Figure 1.—Showing focal area of reticulum hyperplasia with beginning formation of proliferative tubercle ( $\times 400$ ).

and MacMurray. Positive reactions were characterized at 48 hours by a slightly elevated indurated nodule of pale reddish-brown color, varying in size from 0.5 to 1.5 cm. with a larger zone of erythema about the papule.

All patients made uneventful recovery following surgical removal of the enlarged lymph nodes despite extensive suppuration of the nodes and subcutaneous tissues.

#### **PATHOLOGICAL CHANGES**

The lymph nodes that were removed were enlarged and firmly adherent to the surrounding structure. The overlying skin was reddened in the severe cases and the nodes were tender. A variable amount of thin creamy exudate was observed in six cases. In Case 7 about 30 cc. of exudate was aspirated from the lymph nodes and subcutaneous tissues. The lymph nodes with pronounced suppuration were removed piecemeal with fragments of surrounding tissues. In milder cases the lymph nodes were intact. The surfaces of the nodes were roughened and small satellite nodes were usually adherent. The cut surfaces of some of the specimens showed a background of pale gray tissue in which many small discrete pale yellow irregular foci were seen, ranging in size from 2 mm. to 1 cm. in diameter; others showed a moist cut surface of brownish red color in which were seen small opaque foci of gray to light yellow color. The lymph nodes removed after the disease was far advanced were considerably indurated.

Sections were stained with hematoxylin-eosin, Mallory's methyl blue-eosin, Van Gieson's stain, periodic acid leuco-fuchsin reticulum method, trichrome stain of Masson, Mann's methyl blue-eosin, reticulum stain, Giemsa, Feulgen's stain, acid-fast stain, Gram stain and Macchiavello's stain. Sections and smears from all cases were examined for acid-

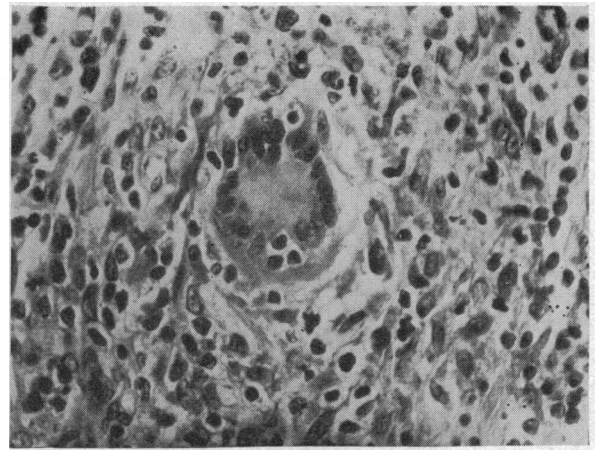


Figure 2.—Small tubercle with central Langhans' giant cell ( $\times 400$ ).

fast organisms, pathogenic fungi and bacteria, with negative findings.

The earliest changes were seen in lymph nodes at ten days following the first signs of tumefaction (Case 6). These consisted of proliferation and swelling of reticuloendothelial cells to form irregular focal aggregates (Figure 1). The aggregates were most numerous in the cortex but the medulla was also involved. These cells, similar to the epithelioid cells seen in tuberculous lesions, had abundant eosinophilic cytoplasm, poorly defined cell borders and large pale-staining nuclei. Small clusters of these cells formed typical miliary tubercles composed of epithelioid cells, occasionally with a central giant cell of Langhans' type (Figure 2). In the centers of the medium-sized and larger aggregates of reticuloendothelial cells, exudation of polymorphonuclear leukocytes and fibrin occurred. In early lesions scattered lymphocytes appeared among the epithelioid cells; but in specimens taken at a later stage of the disease the epithelioid cells in the center of the lesion were replaced by dense masses of leukocytes, at first well preserved in structure but later showing degenerative changes of varying degree mixed with necrotic fragments of epithelioid cells (Figure 3). These degeneration changes were more pronounced at twelve days (Case 4). As a result, abscesses were formed with centers of necrotic cellular and nuclear granular debris surrounded by a well defined zone of epithelioid cells which tended to form a palisade arrangement. Between the epithelioid cell layer and the central zone of necrosis an intermediate layer was usually present, consisting of semi-necrotic epithelioid cells. This layer was of variable thickness and composed of deeply eosinophilic granular debris containing attenuated pyknotic nuclei radiating toward the center. The shapes of the larger lesions were irregular and angular, very similar to the stellate abscesses seen in lympho-

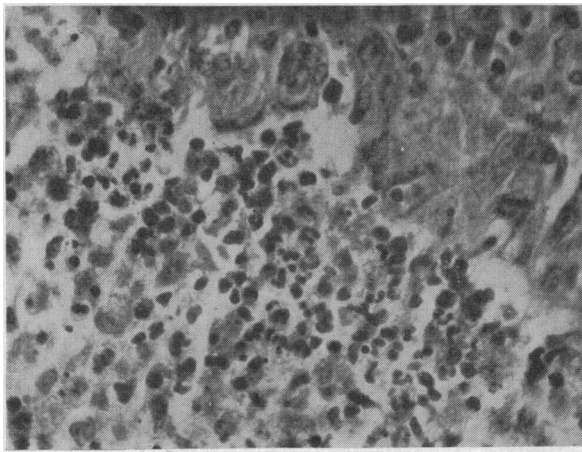


Figure 3.—Small micro-abscess with wall of epithelioid cells ( $\times 400$ ).

granuloma venereum. The smaller lesions were usually round in outline. In the center of the abscesses small remnants of epithelioid cells could be seen, and with the periodic acid reticulum stain the outlines of preexisting vessels were frequently noted. Reticulum fibers were present in the central zone of the early exudative phase but completely destroyed in the later stages.

The abscesses frequently showed conversion of the necrotic central mass into a homogeneous eosinophilic mass, at first patchy but later involving the entire central portion. Fairly well developed lesions of this type appeared at about 25 days. Complete homogenization of the centers of the abscesses was seen only in lesions of 30 to 35 days' duration. With Van Gieson's stain the homogeneous centers stained pale yellow; and when the homogenization was fully developed the staining reaction and appearance of the lesions were identical with the caseous centers of tuberculosis lesions. In well developed caseous lesions four zones were usually present, namely a central zone of caseous necrosis, a thin zone of partial necrosis, a multilayered zone of epithelioid cells arranged in palisades and an outer layer of epithelioid elements arranged circumferentially. About these lesions there were large numbers of plasma cells, moderate numbers of eosinophils and many lymphocytes. Reticulum stains showed a delicate reticulum about the epithelioid cells and coarser fibers and collagenous fibers forming a network at the periphery. In the areas of early exudation considerable reticulum was present which disappeared as these foci became necrotic. However, a zone of collapsed reticulum was usually seen in the region of the junction of the necrotic center and the epithelioid cell layer. With the periodic acid reticulum stain a rather rich vascular network was demonstrated which extended through the zone of epithelioid cells toward the zone of necrosis.

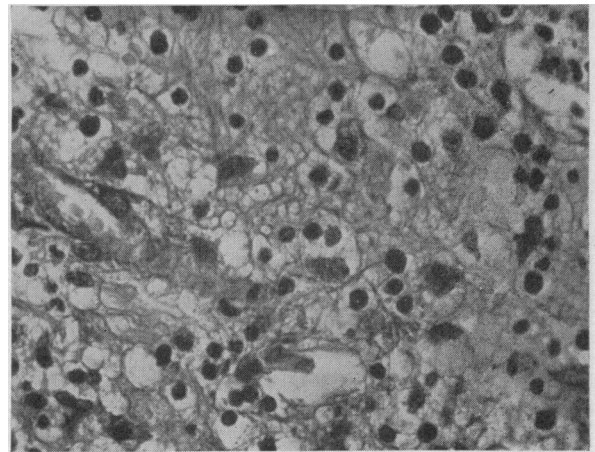


Figure 4.—Diffuse infiltration of histiocytes with foamy cytoplasm ( $\times 400$ ).

Some of the epithelioid foci did not undergo central necrotic changes but persisted as irregular groups of cells which later showed formation of considerable amount of intracellular collagenous fibers. These changes were clearly demonstrated by Van Gieson's stain. In most cases small proliferative miliary tubercles were demonstrable.

An inflammatory reaction extended into the surrounding capsule and fatty tissue of varying degree in all cases studied. Mild involvement consisted of dense foci of lymphocytes, eosinophils and plasma cells, usually perivascular in arrangement. The small veins and arteries showed leukocytic infiltration of the outer layers, fraying of the collagenous fibrils and occasional small thrombi within their lumens. Frequently the tissues about the lesion showed extensive diffuse inflammation with formation of large abscesses usually surrounded by a thin layer of epithelioid cells. Diffuse sheets of histiocytic elements were frequently seen (Figure 4). These often showed abundant foamy vacuolated cytoplasm with sharply defined cell margins. Later fibroblastic proliferation occurred, accompanied by marked proliferation of capillaries. Plasma cells were very abundant. Numerous giant cells of foreign body type were seen in areas of diffuse inflammation. In addition, giant cells of Langhan's type were seen in the wall of the large abscesses. Some of these contained nuclear debris and were located on the inner epithelioid zone immediately adjacent to the central necrotic exudate.

In the older lesions (Cases 1, 5 and 8) extensive fibrous tissue proliferation was seen in the periphery of the necrotic foci surrounding the epithelioid cell zone and extending widely into the surrounding lymphoid tissue. In these areas of fibrosis, considerable infiltration of plasma cells were frequently noted. The lymphoid structures were largely replaced by fibrous tissue. The necrotic centers ap-

peared contracted and were surrounded by a thin layer of epithelioid cells and a wide zone of connective tissue. The radial arrangement of epithelioid cells was retained in some of the lesions and lost in others. Replacement of this layer with fibrous tissue was noted, but there was little evidence of organization of the central caseous areas in the material studied. Calcification was not observed in the necrotic foci.

Only the early stages of healing were present in the material studied (Cases 1, 2, 5 and 8).

*Skin lesions.* In one case the primary lesion of the skin involving the lateral surface of the right thumb was removed. This was a small indolent lesion of violaceous color with a small central crust. A small amount of thin exudate had been expressed from time to time. The duration of this lesion was one month.

Microscopic examination showed the presence of a widespread inflammation involving the corium and the adjacent subcutaneous tissue. Aggregates of lymphocytes, plasma cells and eosinophils were present about the sweat glands, hair follicles and the small blood vessels. Small miliary granulomas were seen directly beneath the epithelium and also in the deeper corium. These consisted of small foci of epithelioid cells among which were many lymphocytes and few eosinophils. One tubercle contained a central giant cell. The epithelial layer showed slight thickening and edema of the deeper layers.

*Inclusion bodies.* Whenever possible, smears were made from unfixed fresh tissues by scraping the surfaces with a knife blade and spreading the material over a glass slide. The smears were fixed in methyl alcohol, corrosive sublimate and by drying. These were stained by Giemsa, Macchiavello's and Feulgen's methods. In smears prepared in this manner a more satisfactory study of cellular inclusions was possible than with fixed tissue sections. With Giemsa stain intracytoplasmic bodies were seen, principally in large reticuloendothelial cells. These were in the form of irregular bodies, some rounded, others of crescent shape with a maximum diameter of about 3 to 5 microns. In addition to these larger bodies there were numerous small rounded forms of fairly regular size and about 0.2 to 0.3 microns in diameter. These stained a light pure blue in contrast to the violet blue of nuclear material. With Macchiavello's stain these bodies took both the blue and red stain; the periphery appeared blue and the central portion showed red coloration. In addition, minute bodies were scattered in the cytoplasm which stained bright red. Other reticuloendothelial cells showed the presence of minute discrete particles smaller than bacteria which were loosely scattered in the cytoplasm. These stained blue with Giemsa. In fixed material both the large and finely divided

bodies were demonstrable in swollen reticuloendothelial cells. With Mann's stain the finely divided granules appeared light purplish red. These bodies did not take the Feulgen's stain for desoxyribose nucleic acid.

#### DISCUSSION

The pathological changes in cat-scratch disease follow a fairly consistent pattern. In study of a number of cases including both early lesions and fairly advanced lesions, the histogenesis of the lesions became apparent. The earliest changes consisted of reticuloendothelial hyperplasia in the form of plaques and small focal clusters. These foci further developed in one of two directions. The most common form was characterized by exudation of polymorphonuclear leukocytes within their centers with the formation of microabscesses, some rounded and others stellate. These abscesses were surrounded by a well-defined zone of epithelioid cells tending to palisade. Less frequently the small aggregates of epithelioid cells did not undergo necrosis but developed into tubercles of proliferative type, many containing central giant cells. These were seen in both the skin and lymph node lesions and often coexisted with suppurative foci.

The abscesses varied considerably in size and often reached large dimensions, especially in the tissues surrounding the involved lymph node. Pronounced degenerative changes occurred in the exudate with the conversion of the exudate into a basophilic granular mass containing nuclear and cellular debris. This granular debris later became hyalinized and stained pink with hematoxylin-eosin and light yellow with Van Gieson's. In this manner solitary and conglomerate tubercles were produced which were often undistinguishable from caseous lesions of tuberculosis. These areas of caseous necrosis coexisted side by side with suppurative foci, and all stages of development were seen in multiple sections of lymph nodes and surrounding tissues in a single specimen. On the basis of cytology the differentiation between this lesion and tuberculosis was frequently difficult, and no doubt in the past many of these nodes were classified as tuberculous inflammations despite lack of demonstrable organisms. The most important finding which served to differentiate this lesion from tuberculosis was the coexistence of an extensive exudative process and proliferative lesions, the former predominating in most instances. However, there were examples in which tubercles, both miliary and solitary, predominated and in these cases differentiation on the basis of morphology alone was indeed difficult.

The histogenesis of the caseative lesions differs in some respects from that of tuberculosis. It is Huebschmann's hypothesis<sup>17</sup> that the earliest phase in the formation of the tubercle is an exudative re-

action associated with tissue injury. From a study of the earliest change in cat-scratch disease, reticulum hyperplasia is the earliest observed reaction; the exudative phase appears later and involves the center of the proliferative foci replacing these cells and forcing them toward the periphery. Necrosis and homogenization of the central exudate then follows. As in tuberculosis, caseous necrosis is bound to the exudative process. This process, however, does not follow the same pattern as Huebschmann describes in tuberculous lesions. It appears from these studies of the lesions of cat-scratch disease that the changes take the following order, namely, proliferative phase, exudative phase and finally the phase of coagulative necrosis, whereas in tuberculosis, according to Huebschmann,<sup>17</sup> the sequence is exudation-caseation-proliferation.

Mollaret and co-workers recognized three phases in the development of the lesions of cat-scratch disease. They observed that the first stage, or "elementary phase," consists of proliferation of reticulo-endothelial cells, the second, or "accentuated phase," is characterized by exudation of leukocytes and formation of micro-abscesses and the third, or "ultimate phase," by formation of large foci of suppuration. Although this in general characterized the manner of development of the exudative process observed in the present series, this classification does not fully explain the development of the proliferative and caseative lesions so frequently observed. Also, all stages of development may be seen in the lymph nodes and surrounding tissues, indicating simultaneous regression and acute exacerbation. In addition, the process may stop at the first phase and heal by fibrosis.

It is difficult to reconcile the observations of the pathological changes in the material studied with those of Winship<sup>27</sup> who, in reporting upon a study of 29 cases, stated that epithelioid cells do not proliferate until abscesses are well developed, whereas the reverse appears to be the case. Also Winship's statement that changes simulating caseous lesions of tuberculosis were not present in cat-scratch disease cannot be accepted on the basis of observations made in material from the present study. In physical appearance and tinctorial characteristics, coagulative necrosis in cat-scratch disease is indistinguishable from the caseous necrosis of tuberculosis.

The differentiation of cat-scratch disease and lymphogranuloma venereum on the basis of gross and histological characteristics is extremely difficult. There is a greater tendency in lymphogranuloma venereum to suppurate and form multiple sinuses, although in cat-scratch disease this may be observed in severe cases. The distribution of the lesions is quite different. The nodes of the upper portion of the body, mainly the epitrochlear, axillary and cervical nodes, are most commonly involved with cat-scratch

disease whereas the inguinal nodes are most frequently involved in lymphogranuloma venereum. Cytological changes are very similar; and the histogenesis is similar in the two diseases. The intermediate zone of partial homogenization of epithelioid elements appears much broader in lymphogranuloma venereum than in cat-scratch disease. In general the tendency to form caseative tubercles is greater in cat-scratch disease than in lymphogranuloma venereum. Despite these differences, the lesions cannot be separated on the basis of histological changes alone. The final diagnosis is dependent on the clinical studies, laboratory tests and skin tests. The striking similarity of the histopathological changes in the two diseases lends additional support to the theory that the causative organisms are closely related.

The ulceroglandular form of tularemia must be differentiated from cat-scratch disease. The early phases of tularemia show focal areas of necrosis bordered by narrow rows of epithelioid cells. Often the epithelioid reaction is insignificant or masked whereas in cat-scratch disease the epithelioid reaction is the initial reaction, with exudation and necrosis of their centers a later development. In the later stages the differentiation between the two conditions may be more difficult. Tubercles with caseous centers and epithelioid cells may develop in both diseases. Lillie and Frances<sup>18</sup> described an inner collagenous zone separating the caseous from the epithelioid pallisades. This is not commonly observed in cat-scratch disease. The clinical and laboratory studies further serve to differentiate these two conditions.

Other conditions such as sporotrichosis, tertiary syphilis, brucellosis and diseases caused by pathogenic fungi must be ruled out by appropriate studies.

The significance and diagnostic importance of intracytoplasmic inclusion bodies is debatable. With Macchiavello's stain these bodies are clearly demonstrable in two forms, namely large irregular plaques 7 to 10 microns in size, and small micrococcoid forms. A matrix was not demonstrable. Despite the fact that the tinctorial reaction and morphologic features of these inclusions are similar to those described in psittacosis by Yamamura and Meyers<sup>28</sup> and in cultures of virus of lymphogranuloma venereum by Rake,<sup>23</sup> final proof that these are specific inclusion bodies must await isolation of the virus and demonstration of similar inclusions in tissue culture.

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